# Toxidrome

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# Outline

- Introduction

1. Cholinergic muscarinic
2. Cholinergic nicotinic
3. Antimuscarinic (anticholinergic)
4. Sympathomimetic
5. Opiate
6. Sedative

# Introduction: Toxidrome

- Toxidrome: Toxic + Syndrome
- Help narrow down possible list of toxin
- If symptoms match -> substance should be on the list
- If symptoms do not match -> don’t try to force it

# Introduction: Toxidrome

- Use signs and symptoms based on receptor
- Majority focus on autonomic nervous system

# Let’s review

# 1. Cholinergic Muscarinic toxidrome

# Muscarinic toxidrome

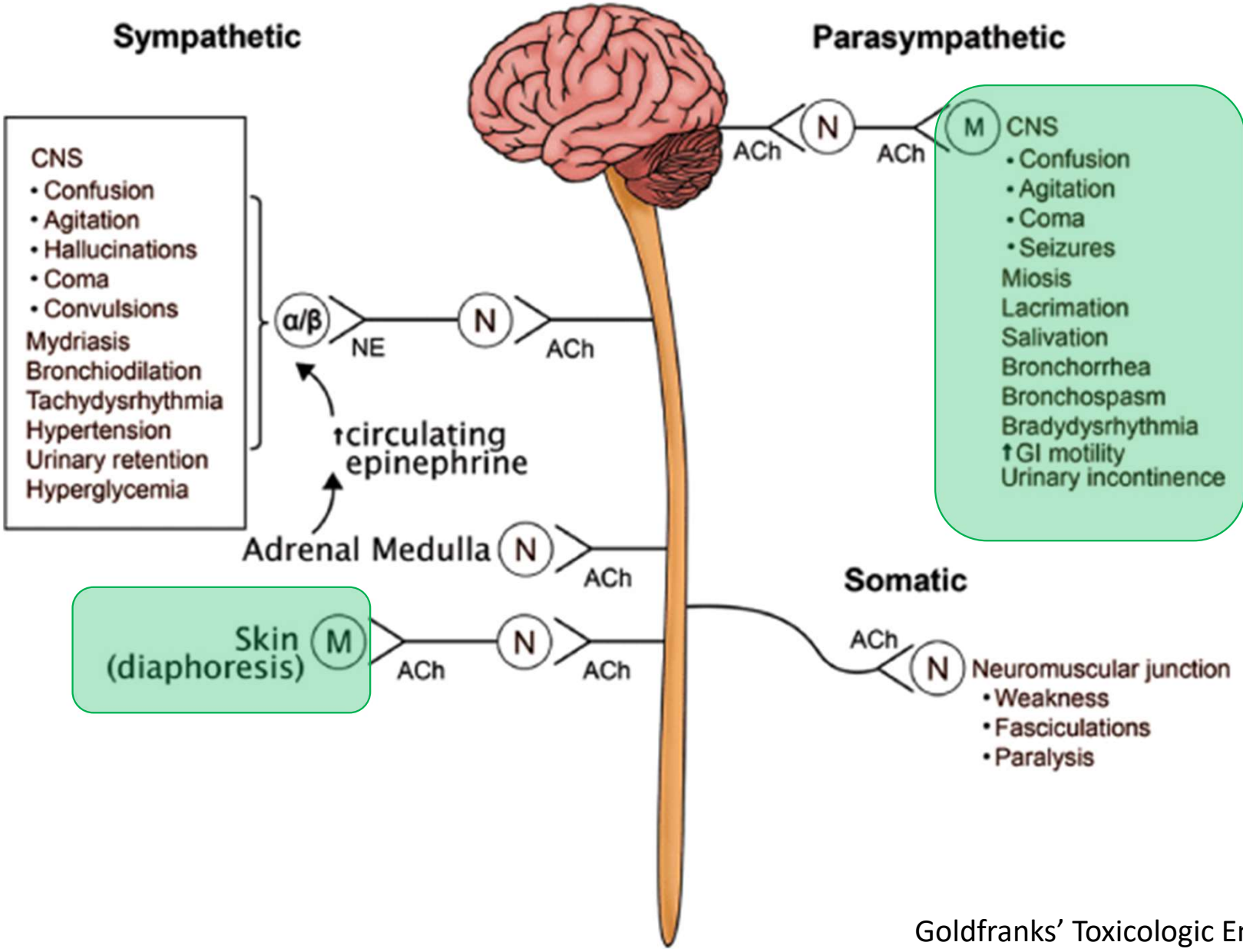
- Symptoms match with agonistic effect on muscarinic receptor (Acetylcholine receptor – muscarinic type)
- M1: CNS, exocrine glands (lacrimal gland, salivary gland, GI, bronchus)
- M2: Heart
- M3: Smooth muscle of GI, bronchus, bladder, Exocrine glands (lacrimal gland, salivary gland, GI, bronchus), Sweat gland, Eye (miosis)
- M4: Brain
- M5: Brain

https://www.ncbi.nlm.nih.gov/books/NBK526134/
https://www.ncbi.nlm.nih.gov/books/NBK555909/

# Muscarinic toxidrome

- Sedate, Agitated, Confused, Seizure, Coma
- Pupil constriction (Miosis)
- **Bronchospasm & Bronchorrhea**
- **↓Heart rate**
- ↑Bowel movement,
  Vomiting, Diarrhea, Defecation
- Urination (bladder contraction)
- Sweating (sympathetic organ with M receptor)

**Give Atropine**




**SLUDGE M BBB**
Salivation,
Lacrimation,
Urination,
Diarrhea,
GI,
Emesis,
Miosis,
**Bradycardia,**
**Bronchospasm,**
**Bronchorrhea**

Goldfranks' Toxicologic Emergency 11th Ed

# Muscarinic toxidrome: substance

- Muscarine (mushroom: Clitocybe, Inocybe)
- Pilocarpine (eyedrop for glaucoma)
- Methacholine (test bronchial hyperresponsive)
- Organophosphorus (cholinesterase inhibitor)
- Carbamate (cholinesterase inhibitor)

# Clitocybe and Inocybe mushroom

Toxicology International

Official Publication of Society of Toxicology

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Toxicol Int. 2013 Jan-Apr; 20(1): 113–115.
doi: 10.4103/0971-6580.111559

PMCID: PMC3702120
PMID: 23833447

## Muscarinic Toxicity Among Family Members After Consumption of Mushrooms

Peter George and Narasimha Hegde

# Clitocybe and Inocybe mushroom

**Table 1: Symptoms and signs recorded in cases with mushroom poisoning**

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Age/sex | 55/female | 52/female | 28/female | 56/male |
| Onset from intake | 2-3 hours | 2-3 hours | 2-3 hours | 3-4 hours |
| Exhaustion | + | + | + | + |
| Irritability | + | + | + | + |
| Convulsions | – | – | – | – |
| Muscular cramps | + | – | – | – |
| Fasciculation | – | – | – | – |
| Salivation/frothing | + | + | + | - |
| Sweating | + | + | + | + |
| Lacrimation | + | + | + | + |
| Blurring of vision | + | + | + | – |
| Miosis | + | + | + | – |
| Ptosis | + | + | + | – |
| Bronchorrhea | + | + | + | – |
| Cough | + | + | + | + |
| Tachypnea | + | + | + | – |
| Rhonchi/Crepts | + | + | + | – |
| Bradycardia | + (34/min) | + (40/min) | + (40/min) | + (44/min) |
| Hypotension (mm Hg) | + (70/40) | + (70/40) | + (70/40) | – (100/60) |
| Abdominal cramps | + | + | + | + |
| Vomiting | + | + | + | + |
| Diarrhea | + | + | + | + |
| Sphincter incontinence | – | – | – | – |

+: Present, –: Absent

# 2. Cholinergic
# Nicotinic toxidrome

# Nicotinic toxidrome

- Symptoms match with agonistic effect on nicotinic receptor (Acetylcholine receptor – nicotinic type)
- N1 (Nm): Skeletal muscle
- N2 (Nn): Neuron (CNS, autonomic ganglion)

https://www.ncbi.nlm.nih.gov/books/NBK526134/

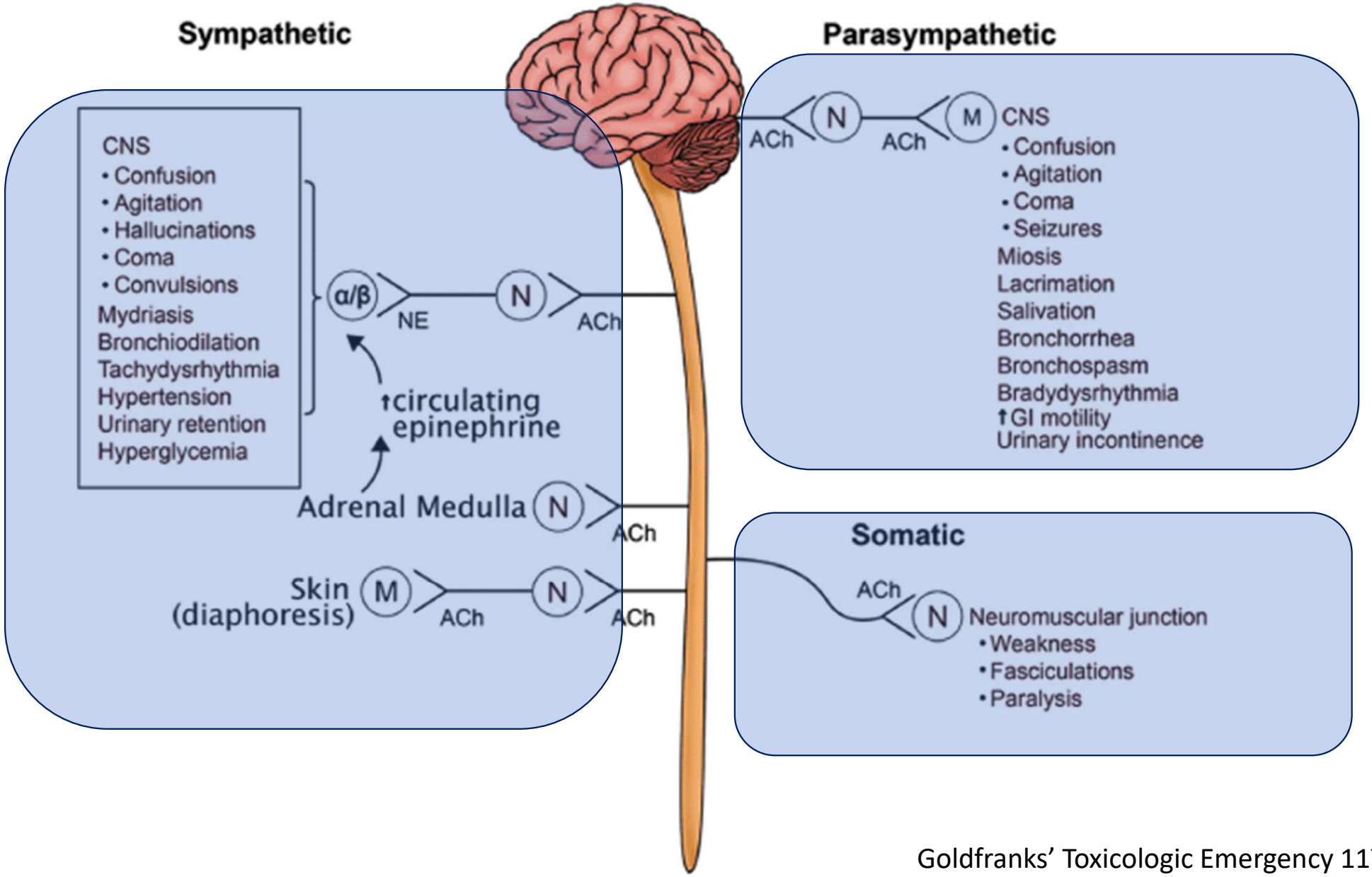
# Nicotinic toxidrome

- Muscle
  M. twitching, Fasciculation, Weakness, Paralysis

- CNS
  Agitated, Confused, Seizure, Coma

- Sympathetic system
  ↑ blood pressure, ↑ heart rate, sweating, pupil dilation

- Parasympathetic system
  Just like muscarinic symptoms
  SLUDGE M BBB

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# Nicotinic toxidrome: substance

- Nicotine
  Tobacco
  Nicotine gum-pill-patch
  E-cigarette fluids
- Succinylcholine (depolarizing neuromuscular blocking agent)
- Organophosphorus (cholinesterase inhibitor)
- Carbamate (cholinesterase inhibitor)

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jkvape.com



# Nicotine poisoning from e-cig fluid

- Burning in the mouth and throat,
- Nausea & vomiting,
- Confusion, dizziness, seizure, coma
- Weakness, fasciculation
- Hypersalivation, & ↑ bronchial secretions, dyspnea
- Early ↑HR & BP
- Late ↓HR & BP

https://www.rcn.org.uk/-/media/Royal-College-Of-Nursing/Documents/Clinical-Topics/ecigarette-vaping-liquid.pdf
https://academic.oup.com/milmed/article/186/1-2/246/5920663
https://www.tandfonline.com/doi/full/10.1080/15563650.2019.1636994

# Nicotine poisoning: Green Tobacco Sickness

- Workers new to handling and harvesting tobacco are high risk (No tolerance to nicotine)
- Workers should wear gloves, long sleeve shirts, long pants and water-resistant clothing


# Nicotine poisoning: Green Tobacco Sickness

- Dizziness, Headache, Seizure
- Salivation
- Nausea, Vomiting, Abdominal pain, Diarrhea
- Muscle cramp, Muscle weakness
- Cough, breathlessness
- Change in blood pressure and heart rate

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763894/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5868082/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1497768/
https://www.osha.gov/green-tobacco-sickness

# Cholinergic toxidrome: Muscarinic + Nicotinic

Cholinesterase inhibitors

Organophosphorus & Carbamate

# Inhibition of Acetylcholinesterase (AChE)

- AChE catalyzes the hydrolysis of acetylcholine (ACh) into choline and acetic acid

- Inhibit AChE leads to accumulation of Ach → ACh excess
- Too much Ach results in overstimulation of Ach receptors
  - Muscarinic receptor
  - Nicotinic receptor

| | Organophosphorus | Carbamate |
|---|---|---|
| **Uses** | Insecticide & warfare agents | Insecticide & medications |
| **Absorption** | Ingestion, Inhalation, Dermal & mucosal contact | |
| **Symptom** | Same | |
| **Onset** | Can be delayed | Early onset |
| **Aging of enzyme** | Yes | No |
| **Specific Mx** | Atropine + 2-PAM | Atropine |
| **Intermediated syndrome** | Yes | No |
| **Peripheral neuropathy (chronic)** | Yes | No |

# Organophosphorus

- Insecticide (solution or emulsified concentrate liquid)
- Warfare agent: sarin, soman, Vx


chlorpyrifos 40% w/v EC


malathion 50% w/v EC


Tokyo attacked by “Sarin Gas” (Mar 1995)

# Carbamates

- Insecticides:
  soluble powder, granule, solution, or emulsified concentrate liquid
- Plant: Calabar bean (*Physostigma venenosum*)
- Medications: physostigmine, pyridostigmine, rivastigmine, galantamine

**methomyl 40% SP**


**methomyl 18% w/v SL**


**carbofuran 3% GR**

# Toxidrome (1)

| Toxidrome | Cholinergic Muscarinic | Cholinergic Nicotinic |
|---|---|---|
| **Vital signs** | **↓HR, ↓BP** | ↑HR, ↑BP |
| **Mental Status** | Lethargy-coma | Agitated, seizure |
| **Other effect** | **Salivation**,<br>**Lacrimation,**<br>Urination,<br>Diarrhea,<br>Vomiting,<br>Diaphoresis,<br>**Miosis**<br>**Brobchorrhea**<br>**Bronchospasm** | **Fasciculation**<br>**Weakness**<br>**Paralysis**<br><br>Also cause muscarinic symptoms |
| **Substances** | Pilocarpine<br>Muscarine<br>Organophosphorus<br>Carbamates | Tobacco, Nicotine products<br>Succinylcholine<br>Organophosphorus<br>Carbamates |

# 3. Antimuscarinic toxidrome

(also called anticholinergic toxidrome)

# Antimuscarinic toxidrome

- Symptoms match with antagonistic effect on muscarinic receptor
- Delirium, Confused
- ↑Heart rate
- Flushing
- Dry mouth, mucosa, and skin (no sweating leads to ↑ body temperature)
- Pupil dilation
- ↓ Bowel movement, ↓ bowel sound, and full bladder

- Antidote: Physostigmine (carbamate med; not available in Thailand)

# Antimuscarinic toxidrome: substance (1)

- Pure antimuscarinics
  Atropine, scopolamine, hyoscine, hyoscyamine
  (antimuscarinic plant also contain these substances)

# Antimuscarinic plants

- Use as hallucinogen
- *Datura stramonium.*
  “Jimson weed” or “devil’s trap”

- *Brugmansia spp.*
  “Angel’s trumpet” or “Lum Phong”

- Atropa belladonna
  “Deadly nightshade”

# Antimuscarinic toxidrome: substance (2)

- Substance with antimuscarinic, sedative, and other effects
  - Tricyclic antidepressants: amitriptyline, nortriptyline, imipramine
  - Antihistamines: chlorpheniramine, promethazine, cetirizine
  - Antipsychotics: haloperidol, risperidone, olanzapine

- Other effects
  - Histamine-1 receptor antagonist: sedation (TCA, antihistamines, antipsychotic)
  - **Cardiac & neuron sodium channel blockade** (TCA, some antihistamines)
  - Cardiac Potassium channel blockade (TCA, antipsychotics)
  - Alpha adrenergic-1 receptor antagonist: vasodilation (TCA, antipsychotics)

# Wide QRS + Tall R in aVR

## Cardiac Na channel blockade

# Cardiac Na channel blockade

- Wide QRS: antiarrhythmic Ia, Ic (NOT Ib), Carbamazepine, Lamotrigine, Diphenhydramine, Cocaine, Propranolol, and Quinine

- Ia: **Wide QRS** + marked QT prolong
  quinidine, hydroquinidine, disopyramide, procainamide

- Ib: Normal QRS and shorten QT
  lidocaine, phenytoin and mexiletine

- Ic: **Wide QRS** + QT prolong
  flecainide, encainide, propafenone and aprindine

http://cdn.intechopen.com/pdfs/26834.pdf

# 4. Sympathomimetic toxidrome

# Sympathomimetic toxidrome

- Symptoms match with sympathetic overactivity
- CNS: agitation, confused, hallucination, seizure, coma, excited delirium

- Sympathetic system:
  ↑Heart rate (beta-1), ↑Blood pressure & vasoconstriction (mainly alpha-1)
  ↑Body temperature
  Sweating
  Pupil dilation (alpha-1)
  Variable bowel movement
  (alpha-1 & beta-1 increase; beta-2 & low serum K decrease)

- Others: tremor, choreoathetosis

https://www.ncbi.nlm.nih.gov/books/NBK532904/

# Sympathomimetic toxidrome: substances

- Amphetamine & derivatives
- Cocaine (Na channel blockage)
- Theophylline & , Caffeine (Dialyzable)
- Thyroid hormone
- Alcohol withdrawal
- Sedative withdrawal

# Toxidrome (2)

| Toxidrome | Anticholinergic | Sympathomimetic |
|---|---|---|
| **Vital signs** | **↑HR, ↑ BP**, ↑T | **↑HR, ↑ BP**, ↑T |
| **Mental status** | Agitation<br>Delirium<br>Hallucination | Hyperactive<br>Psychosis, agitation<br>Seizure |
| **Symptoms** | **Dry skin & mucosa**<br>Mydriasis<br>**↓↓ Bowel movement**<br>**Bladder retention** | **Diaphoresis**<br>Mydriasis<br><-> Bowel movement<br>Tremor |
| **Substances** | Anticholinergics<br>Antihistamines (+)<br>Tricyclic antidepressants (+)<br>Antipsychotics (+) | Amphetamines, Cocaine (+)<br>Theophylline, Caffeine<br>Theroid hormone<br>Alcohol & sedative withdrawal |

# 5. Opiate toxidrome

# Opiate toxidrome

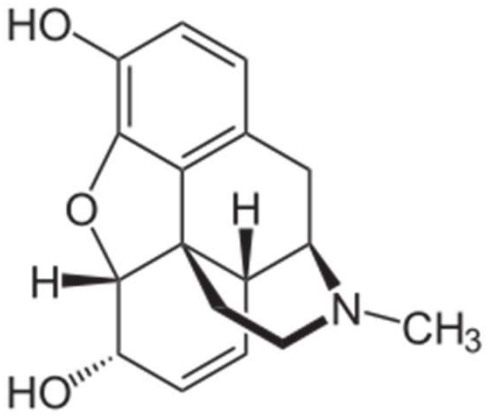
- Symptoms match with mu-opioid agonist effect
- Mu-receptor agonistic effects:
  Analgesia, Euphoria
  Sedation, Coma
  **Respiratory depression**, Cough suppression
  Pin-pointed pupil (miosis),
  ↓ Heart rate
  ↓ GI motility

# Opiate toxidrome: substances

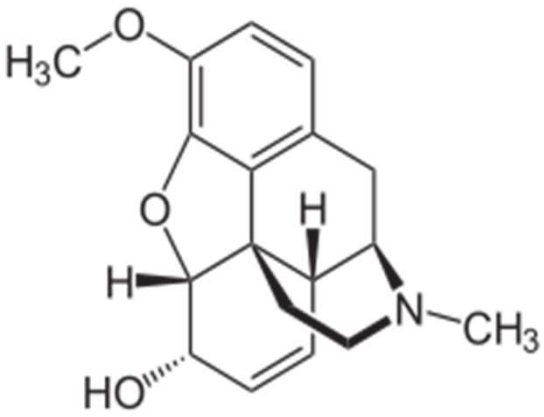
- Opioids: Morphine, Codeine, Heroin, Tramadol, Fentanyl
- Substances with opioid effects: Kratom, Dextromethorphan
- Other substances/conditions those suppress respiratory center and have CNS depression effect
  - Alpha-2 adrenergic agonist (sympatholytic): Clonidine, Methyldopa, Xylazine
  - GABA-B agonist: Baclofen, Gamma hydroxybutyrate (GHB)
  - High dose sedatives: Phenobarbital, Ethanol
  - Brainstem lesion

# Opioid

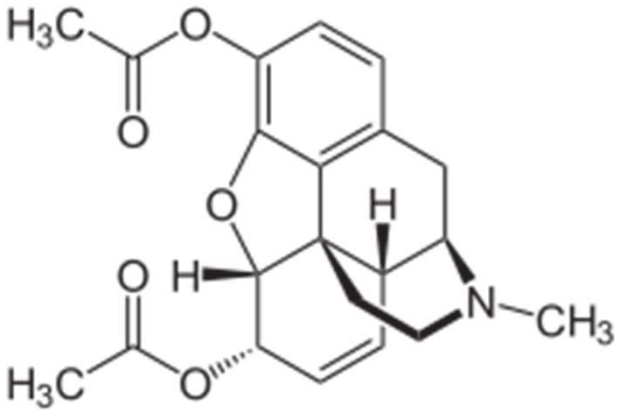
- Opiates: morphine, codeine
- Semisynthetic: heroine, oxycodone, hydrocodone
- Synthetic: meperidine, fentanyl, tramadol, buprenorphine, methadone




morphine



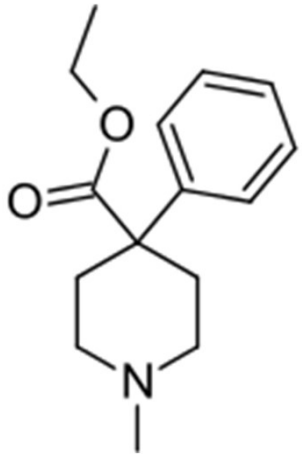

codeine



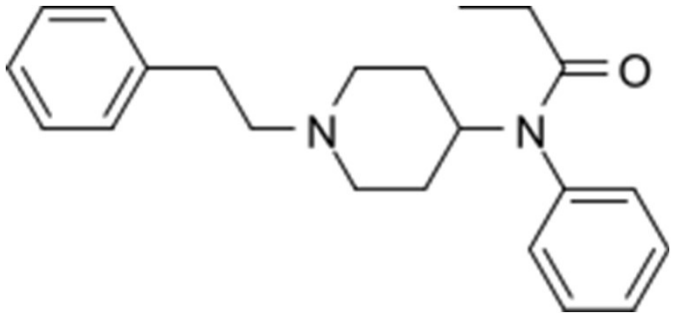

heroine

# Opioid

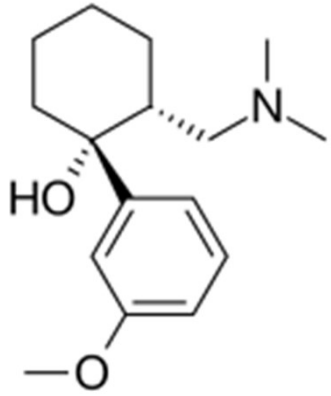
- Opiates: morphine, codeine
- Semisynthetic: heroine, oxycodone, hydrocodone
- Synthetic: meperidine, fentanyl, tramadol, buprenorphine, methadone



meperidine



fentanyl



tramadol

# Opiate toxidrome: substances

- Mu opioid receptor
- Alpha-2 adrenergic receptor
- GABA-B receptor

All are G protein coupling receptors causing
- Inhibition of cAMP & PKA pathway
- ↑K efflux
- ↓Ca influx

Overall cause hyperpolarization and inhibitory effect

Naloxone (mu-opioid antagonist) is reported to
- Work well for reversing respiratory depression in opioid, kratom, dextromethorphan overdose
- Variably (not always) reverse respiratory depression effect in alpha-2 agonist overdose
- No response in baclofen or GHB overdose

# Opiate toxidrome: substances

- Opioids: Morphine, Codeine, Heroin, Tramadol, Fentanyl
- Substances with opioid effects: Kratom, Dextromethorphan

Response to Naloxone

- Other substances/conditions those suppress respiratory center and have CNS depression effect
  - Alpha-2 adrenergic agonist: Clonidine, Methyldopa, Xylazine
  - GABA-B agonist: Baclofen, Gamma hydroxybutyrate (GHB)
  - High dose sedatives: Phenobarbital, Ethanol
  - Brainstem lesion

# 6. Sedative toxidrome

# Sedative toxidrome

- CNS depression
- Normal blood pressure, heart rate,
  body temperature, respiratory rate

- Can be from hyperpolarization of cells
  GABA-A receptor stimulation
  Lower dose of substances those cause opiate toxidrome

# Sedative toxidrome

- GABA-A receptor direct stimulation
  - GABA
  - Muscimol (mushroom)
  - Propofol
  - Barbiturate (high-dose phenobarbital)
  - Topiramate

- GABA-A receptor positive allosteric
  - Benzodiazepine
  - Alcohols
  - Chloroform
  - Inhale anesthetic (isoflurane, sevoflurane)
  - Z-drugs (zolpidem, zopiclone zaleplon)
  - Propofol
  - Barbiturate

# Toxidrome (3)

| Toxidrome | Opiates | Sedatives |
|---|---|---|
| **Vital signs** | ↓**RR**, ↓ BP, ↓T | Normal HR, BP, T |
| **Mental status** | Lethargy, coma | Lethargy, coma |
| **Symptoms** | **Miosis**<br>**Apnea**<br>↓↓ Bowel movement | Normal pupil,<br>Normoactive bowel sound |
| **Substances** | Opiates<br>Phenobarbital, Baclofen<br>Ethanol, Isopropanol<br>Methyldopa, Clonidine, Xylazine (sympatholytic drugs)<br>Pon & Cerebellum lesion | Benzodiazepine<br>Z-drugs (zolpidem, zopiclone zaleplon)<br>Lower dose of substances cause opiate toxidrome |

| | CNS | T | HR & BP | RR | Bronchus, Bowel, & Bladder | Secretion | Sweating | Pupil |
|---|---|---|---|---|---|---|---|---|
| Cholinergic muscarinic | ↓↔ | ↔ | ↓↓ | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↓↓ |
| Cholinergic nicotinic | ↑↔ | ↔ | ↔↑↓ | ↑↑ | ↔↑ | ↔↑ | ↑↑ | ↑↓ |
| Antimuscarinic | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↓↓ | ↓↓ | ↓↓ | ↑↑ |
| Sympathomimetic | ↑↑ | ↑↑ | ↑↑ | ↑↑ | ↔↑↓ | ↓↓ | ↑↑ | ↑↑ |
| Opiate | ↓↓ | ↓ ↔ | ↓↓ | ↓↓ | ↓ ↔ | ↓ ↔ | ↓ ↔ | ↓↓ |
| Sedative | ↓↓ | ↔ | ↓ ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

# Other insecticides

- **Organochlorine** (DDT, Lindane, Endosulphan)
  Inhibit GABA receptor & open Na channel
  Seizure (status epilepticus) & cardiac tachyarrhythmia
  Mx: benzodiazepine, Phenobarbital, Propofol

- **Pyrethroid** (cypermethrin, pyrethrin, permethrin)
  Less injury to mammal cell
  Allergy; angioedema, anaphylaxis (human)
  Salivation (human & animal), tremor & choreoathetosis (animal)
  Mx: Supportive

- **Avermectin** (abamectin, emamectin)
  ↑ GABA modulation, ↑Nitric oxide production
  Alteration of consciousness, coma (rarely seizure may be from hypoxia), BP drop
  Mx: Supportive

# Other Herbicides

- **Paraquat**
  Bipyridyl herbicide >> radical and oxidative injury
  Renal, Liver, Lung; can be tested by "urine dithionite test"
  Mx: No O2, give Dexa, cyclophos, antioxidants

- **Glyphosate**
  Surfactant may explain toxicity than glyphosate itself
  GI symptom, Renal injury, Cardiomyopathy (CHF)
  Mx: supportive

- **Chlorophenoxy compound** (2,4-D)
  Uncoupling of oxidative phosphorelation
  Rhabdomyolysis, renal failure, hyperthermia, encephalopathy
  Mx: Enhance elimination by *alkalinize urine*
  *Hemodialysis* may remove the substance & shortening clinical course

- **Anilide** (propanil) **& Chloroacetanilide** (Butachlor)
  Oxidant induced hemolysis, methemoglobin, hepatitis
  Mx: Supportive, blood transfusion for anemia,
  methylene blue for methemoglobinemia,
  NAC 150 mg/kg in 1-3 h then 300 mg/kg/d as antioxidant

# Other rodenticides & fumigants

- **Warfarin and superwarfarin:** Vitamin K antagonist
  Delayed onset coagulopathy
  Mx serial PT INR at 24-48h (warfarin), every 6-8 h for 48 h (superwarfarin)
  Vitamin K, FFP, PCC, FEIBA (activated PCC), Factor VIIa

- **Strychnine (แสลงใจ):** Glycine antagonist at spinal cord
  Spinal seizure; onset 0.5-1 h (DDx with tetanus)
  Mx supportive care (recov around 24-48h)

- **Tetramine:** GABA antagonist
  Status epilepticus
  Mx: benzos >> phenobarbital, propofol

- **Phosphide** react with water>>phosphine gas (toxic form-oxidative injury); "**Do not lavage**"
  Delayed onset metabolic acidosis, ARDs, Cardiomyopathy, multiorgan failure
  Mx: gastric aspiration, charcoal is OK, ??feed coconut oil??
  Steroid, Magnesium, NAC, High dose insulin, ??intralipid emulsion??

# Others

- Hyperthermia
  - Serotonin syndrome
  - Neuroleptic malignant syndrome
  - Heat stroke
  - Malignant hyperthermia
  - Malignant catatonia
- Ketamine (NMDA antagonist)
- Kratom (Mitragynine; low dose = stimulant; high = dose opioid)
- Laughing gas
- Cannabis